REMARKS

Status of the claims

Claims 1, 26-32, and 34 are pending in this application. Claims 30-31 have been withdrawn as allegedly directed to non-elected inventions and species. Claims 1, 26-29, 32 and 34 are currently under consideration, and all have been rejected on a variety of grounds. Claims 36-37 are newly presented. Newly presented claims 36-37 are supported in the Substitute Specification filed on November 1, 2001, in response to a Notice to File Corrected Application Papers, on page 9, line 7 to page 10, line 2; p. 12, lines 13-19; and p. 13, line 20 to p. 14, line 8. No new matter is added by these amendments. After entry of this amendment, claims 1, 26-32, 34, and 36-37 will be pending.

Formal matters

Applicants have amended the specification to include a "Brief Description of the Drawings" section, in accord with MPEP § 608.01(f). These amendments introduce no new matter. Support for these amendments is in the Substitute Specification filed on November 1, 2001, in response to a Notice to File Corrected Application Papers, for example from page 15, line 6 to page 17, line 2, and from page 29, line 20 to page 33, line 10. Applicants thank the Examiner for pointing out this inadvertent omission from the Substitute Specification as filed.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 26-29, 32 and 34 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking a written description of the claimed invention sufficient

to reasonably convey to one of ordinary skill in the art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner alleges that the originally filed specification does not support the limitation in claims 1 and 28 of "determining said mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes." Office Action of 04/21/05, p. 5 (emphasis in original). The Examiner further alleges that (1) the specification "does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned 'limitation'" and (2) the limitations recited in the pending claims allegedly introduce new concepts, thereby violating the written description requirement of § 112, first paragraph. *Id.*

The Examiner claims that specification page 34, lines 5-10—the passage cited for support in Applicants' response of March 25, 2005—consists only of a listing of references that does not provide the needed support. Applicants respectfully direct the Examiner to the Substitute Specification filed with the Office on November 1, 2001, in response to a Notice to File Corrected Application Papers. Page 34, lines 5-10 of the Substitute Specification includes the following text:

> Moreover, our findings may offer a new approach to treat pathologic conditions in humans that are associated with abnormal generation or function of CTL. For example, the ability to selectively modify this critical step might be useful to enhance CTL killer function during viral infection or to combat tumors, whereas CTL suppression might be beneficial for the treatment of autoimmune diseases.

Applicants respectfully submit that the quoted passage adequately supports the limitation of claims 1 and 28 by presenting an advantage of the claimed invention over

existing methods of treatment, and by suggesting different circumstances in which manipulating CTL differentiation to enhance or suppress CTL activity would be useful.

Furthermore, the specification includes numerous examples of CTL activity assays conducted following vaccinia virus infection in normal, wild-type animals, and in mice lacking fucosyltransferase (FT). FT-deficient mice also lack biologically active PSGL-1, because PSGL-1 function requires fucosylation at specific sites. *See, e.g.,* Substitute Specification p. 9, line 6 to p. 10, line 2; p. 12, lines 13-19; and p. 13, line 20 to p. 14, line 8. Animals lacking FT and PSGL-1 are characterized by abnormal generation or function of cytotoxic T lymphocytes. Applicants respectfully submit that the limitation in question does not introduce new concepts in violation of the written description requirement, and that the specification provides sufficient direction for the claimed methods including the above-mentioned limitation. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1, 26-29, 32 and 34 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner objects to the phrase "determining said mammalian subject has a condition associated with abnormal generation or function of cytotoxic T lymphocytes," and alleges that the terms "abnormal generation or function" and "associated with" are ambiguous or ill-defined. The Examiner further alleges that one of ordinary skill in the art "would not be reasonably apprised of the metes and bounds of the invention" because the specification allegedly fails to define (1) what constitutes "abnormal generation or function of cytotoxic T lymphocytes," (2)

what defines "associated," and (3) what assays or endpoints are determined by the claimed method step. Office Action of 04/21/05, p. 5.

Without acquiescing to the Examiner's contention that the term "abnormal generation or function" is ambiguous or ill-defined, and solely in an effort to further prosecution, Applicants have amended claims 1 and 28 to recite "determining said mammalian subject has a condition characterized by elevated CTL activity." The Examiner also alleges that the term "associated with" is ambiguous or ill-defined. Without acquiescing to the Examiner's contention that the term "associated with" is ambiguous or ill-defined, and solely in an effort to further prosecution, Applicants have amended claims 1 and 28 to recite "conditions characterized by elevated CTL activity." Applicants believe these amendments obviate this rejection, and therefore respectfully request that it be withdrawn.

Rejection under 35 U.S.C. § 102(e)

Cummings *et al.*

Claims 1, 26-29, 32 and 34 stand rejected under 35 U.S.C. § 102(e), as allegedly anticipated by U.S. Patent No. 6,667,036, issued to Cummings *et al.* ("Cummings"). The Examiner further cites U.S. Patent No. 5,747,036, issued to Brenner *et al.* ("Brenner") in support of the proposition that rheumatoid arthritis was known to be a condition associated with abnormal generation or function of CTLs. The Examiner alleges that the combination of Cummings and Brenner anticipates the claimed invention because (1) "it does not appear that the claim language or limitations result in a manipulative difference in the method steps" compared to the prior art; and (2) the

claims "do not require an actual determination of CTL function *per se*." Office Action of 04/21/05, pp. 6-7.

Applicants respectfully traverse this rejection. To anticipate a claim, a single prior art reference must disclose "each and every element as set forth in the claim . . . either expressly or inherently." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP § 2131 (8th ed., 2d revision, 2004). The identical invention must be disclosed "in as complete detail as is contained in the . . . claim" at issue. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, (Fed. Cir. 1989); MPEP § 2131. A 35 U.S.C. § 102(e) rejection over multiple references may be proper if the additional references "are cited to (1) prove the primary reference contains an 'enabled disclosure;' (2) explain the meaning of a term used in the primary reference; or (3) show that a characteristic not disclosed in the reference is inherent." MPEP §2131.01. The Examiner cites Brenner "as an evidentiary reference" in support of the assertion that "the ordinary artisan recognized that rheumatoid arthritis was known to be associated with the generation and function of CTLs at the time the invention was made." Office Action of 04/21/05, p. 7.

Cummings claims (1) methods of treating rheumatoid arthritis, adult respiratory distress syndrome, and ischemic injury, and (2) a method of inhibiting leukocyte binding to activated platelets or endothelial cells, all by administering an effective amount of a PSGL-specific antibody. Cummings discloses determination of the effective dose of PSGL antibodies to prevent extension of myocardial infarction, acute respiratory distress syndrome, shock (low blood pressure), stroke, and organ transplant rejection. Cummings also discloses the administration of PSGL antibodies to a subject followed

by assessment of a clinical response. Brenner teaches that a subset of patients afflicted with rheumatoid arthritis exhibit increased expression of a particular T cell receptor alpha chain variable region, Vα12.1, that activated CD8+ cytotoxic lymphocytes are present in patients with rheumatoid arthritis, and discloses monoclonal antibodies specific for the Vα12.1 epitope on such CTLs.

Because Cummings, either alone or in combination with Brenner, does not disclose each and every element of the claimed invention, even under the Examiner's "broadest reasonable interpretation" of the claimed methods, Applicants respectfully assert that neither Cummings alone, nor the combination of Cummings and Brenner can anticipate the claimed invention. Without acquiescing to the Examiner's contention that the combination of Cummings and Brenner anticipates the claimed invention, and solely in an effort to further prosecution, Applicants have amended the claims to include a step of assaying CTL activity. The specification contains ample support for such assays in peritoneal exudate lymphocytes (PEL). *See, e.g.,* Substitute Specification p. 9, line 6 to p. 10, line 2; p. 12, lines 13-19; and p. 13, line 20 to p. 14, line 8. Applicants believe these amendments obviate this anticipation rejection, and therefore respectfully request that it be withdrawn.

Larsen *et al.*

Claims 1, 26-29, 32 and 34 stand rejected under 35 U.S.C. § 102(e), as allegedly anticipated by U.S. Patent No. 6,277,975, issued to Larsen *et al.* ("Larsen"). The Examiner further cites Brenner in support of the proposition that rheumatoid arthritis was known to be a condition associated with abnormal generation or function of CTLs.

The Examiner alleges that the combination of Larsen and Brenner anticipates the claimed invention because (1) "it does not appear that the claim language or limitations result in a manipulative difference in the method steps" compared to the prior art; and (2) the claims "do not require an actual determination of CTL function *per se*." Office Action of 04/21/05, p. 8.

Applicants respectfully traverse this rejection. Larsen teaches the use of a variety of PSGL fusion proteins which interfere with P-selectin binding and leukocyte adhesion to endothelial cells for treating a variety of conditions, including inflammatory disorders, autoimmune diseases, transplantation rejection and tumor metastases. Larsen also teaches that monoclonal antibodies specific for PSGL may be useful therapeutics for treatment of both inflammatory diseases and cancer, when abnormal expression of PSGL is involved. Brenner teaches that a subset of patients afflicted with rheumatoid arthritis exhibit increased expression of a particular T cell receptor alpha chain variable region, Vα12.1, that activated CD8+ cytotoxic lymphocytes are present in patients with rheumatoid arthritis, and discloses monoclonal antibodies specific for the Vα12.1 epitope on such CTLs.

Because Larsen, either alone or in combination with Brenner, does not disclose each and every element of the claimed invention, even under the Examiner's "broadest reasonable interpretation" of the claimed methods, Applicants respectfully assert that neither Larsen alone, nor the combination of Larsen and Brenner can anticipate the claimed invention. Without acquiescing to the Examiner's contention that the combination of Larsen and Brenner anticipates the claimed invention, and solely in an effort to further prosecution, Applicants have amended the claims to include a step of

assaying CTL activity. The specification contains ample support for such assays in peritoneal exudate lymphocytes (PEL). *See, e.g.,* Substitute Specification p. 9, line 6 to p. 10, line 2; p. 12, lines 13-19; and p. 13, line 20 to p. 14, line 8. Applicants believe these amendments obviate this anticipation rejection, and therefore respectfully request that it be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 26-29, 32 and 34 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Cummings and/or Larsen, in view of Snapp *et al.* (Blood 91:154-164 (1998)) ("Snapp"), Diacovo *et al.* (J. Exp. Med. 183:1193-1203 (1996)) ("Diacovo"), Raychaudhuri *et al.* (U.S. Patent No. 6,270,769) ("Raychaudhuri"), Rooney *et al.* (U.S. Patent No. 5,962,318) ("Rooney"), and further in view of Brenner.

The Examiner contends: (1) that Cummings teaches "methods of inhibiting various inflammatory conditions, including rheumatoid arthritis," with antibodies that bind PSGL, and further notes that "rheumatoid arthritis is an autoimmune disease, [so] the prior art teaching of a species reads on the claimed genus" (Office Action of 04/21/05, p. 11); (2) that Larsen teaches methods of treating a variety of conditions, including inflammatory disorders and autoimmune diseases, with antibodies that neutralize PSGL, including monoclonal antibodies and antibody fragments; (3) that Snapp teaches all T cells, including CD8+ T cells, express high levels of PSGL-1, and that PSGL-1 is the principal or sole ligand for P-selectin on T cells; and (4) that Diacovo teaches that PSGL mediates P-selectin-dependent adhesion on myeloid cells, is present on α/β T cells, on which it "may serve a similar function," and that anti-PSGL-1 antibodies

completely inhibit binding of purified P-selectin to neutrophils and peripheral blood T lymphocytes (Office Action of 04/21/05, p. 11). The Examiner further cites Raychaudhuri for teaching "the known methods of determining CTL function," and Rooney for teaching "methods of monitoring CTL function." *Id.* at p. 12.

Finally, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made "to apply the teachings of Snapp et al. and Diacovo et al. to those of Cummings et al. AND/OR Larsen et al to determine the ability of anti-PSGL-1 antibodies to modulate or inhibit the functions, including CTL functions of said CD8+ T cells." *Id.* Further, the Examiner argues that, "[g]iven the number and types of diseases and conditions targeted by Cummings et al. and Larsen et al., one of ordinary skill in the art would have been motivated to monitor the ability of anti-PSGL-1 antibodies to inhibit various immune responses, including the immune responses of cells expressing PSGL-1, including CD8+ T cells." *Id.*

The Claimed Invention Is Not *Prima Facie* Obvious

Applicants respectfully traverse this rejection. The Patent Office bears the burden to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Fine,* 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995). To support a rejection under § 103, the examiner must provide evidence showing "as a whole" that the legal determination sought to be proved is more probable than not. MPEP § 2142. To satisfy this burden, the Office must first demonstrate some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art references, or

to combine the relevant teachings from the references. *Fine,* 837 F.2d at 1074; MPEP § 2143. Next, the Office must show that one of ordinary skill in the art would have had a reasonable expectation of success on modifying the prior art references, or on combining the relevant teachings from the references. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion or motivation and the reasonable expectation of success *"must be founded in the prior art, not in the applicant's disclosure." Id.* (emphasis added). Finally, the Office must show that the combined prior art references "teach or suggest all the claim[ed] limitations." MPEP § 2143.

The Examiner bears the initial burden of providing "some suggestion of the desirability of doing what the inventor has done." MPEP § 2142. To prove that a claimed invention is, more probably than not, obvious, the cited references "must expressly or impliedly suggest the claimed invention" with all its limitations, or the examiner "must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985); MPEP § 2142. Applicants respectfully submit that the Examiner has failed to meet this initial burden.

The Combined References Do Not Teach or Suggest the Claimed Invention With All Its Limitations

In contrast to the cited combination of Cummings and Larsen with Snapp, Diacovo, Raychaudhuri, Rooney, and Brenner, the claimed invention as amended herein teaches methods of inhibiting the cytotoxic response of a T lymphocyte in mammalian subjects by (1) determining a subject has a condition characterized by

elevated CTL activity by assaying said activity, and (2) treating such a subject with a PSGL-specific antibody. Neither Cummings or Larsen teaches or suggests determining a mammalian subject has a condition characterized by elevated CTL activity by assaying said activity, either explicitly or implicitly.

Applicants respectfully note that, as discussed above, Snapp teaches that all T cells express high levels of PSGL-1, and that a PSGL-1-specific monoclonal antibody inhibits binding of P-selectin to PSGL-1. Snapp does not teach assaying CTL activity, either in cell culture, or as a disease marker in a subject. Snapp also fails to provide any motivation or suggestion that a PSGL-specific antibody would be useful for inhibiting the cytotoxic response of a T lymphocyte, or for the treatment of a disease or condition resulting from elevated CTL activity. Diacovo does not remedy the deficiencies of Cummings and Larsen. Like Snapp, Diacovo does not teach assaying CTL activity, either in cell culture, or as a disease marker in a subject. Similarly, Diacovo does not teach or suggest that using a PSGL-1-specific antibody would be useful in inhibiting elevated CTL activity.

The Examiner cites Raychaudhuri and Rooney for providing "the known methods of testing CTL responses, including in response to immunosuppressive antibodies." Office Action of 04/21/05, p. 12. Applicants respectfully note that both Raychaudhuri and Rooney teach methods of inducing CTL responses in both healthy and immuno-compromised individuals to treat a wide range of viral infections, as well as cancer, malaria, and other disorders. While both references also teach methods for assaying CTL activity, neither monitors such activity as a disease marker (i.e., elevated CTL activity due to a disease state), but only to determine whether the methods of treatment

claimed therein were effective at stimulating cell-mediated immunity. Because neither Raychaudhuri nor Rooney teaches (1) determining a mammalian subject has a condition characterized by elevated CTL activity by assaying said activity, or (2) treating said condition by administering a therapeutically effective amount of an antibody directed to PSGL-1, neither reference compensates for deficiencies in the teachings of Cummings, Larsen, Snapp or Diacovo. Thus the Examiner has failed to establish a *prima facie* case of obviousness because the cited combination of references fails to teach or suggest each and every limitation of the claimed invention as amended herein.

No Motivation Existed To Combine The References

When the motivation to combine the teachings of the references is not immediately apparent, "it is the duty of the examiner to explain why the combination of the teachings is proper." *Ex parte Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986); MPEP § 2142. To satisfy this duty, "the examiner must indicate the reasons *why* one skilled in the art" would have been motivated to combine the references. *Id.* (emphasis in original).

Here the Examiner offers only the bare assertion that one of ordinary skill in the art would have been motivated to combine the teachings of Cummings and Larsen with the teachings of Snapp and Diacovo because, "[g]iven the number and types of diseases and conditions targeted by Cummings et al., and Larsen et al., one of ordinary skill in the art would have been motivated to monitor the ability of anti-PSGL-1 antibodies to inhibit various immune responses, including the immune responses of cells expressing PSGL-1, including CD8+ T cells." Office Action of 04/21/05, p. 12.

This conclusory statement neither clearly explains the Examiner's argument that a skilled artisan would have been motivated to combine the references, nor demonstrates that the combined references expressly or impliedly suggest the claimed invention with all its limitations. Therefore Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Applicants respectfully submit that there was no motivation to combine the teachings of Cummings and Larsen with the teachings of Snapp or Diacovo. Cummings teaches methods of inhibiting various inflammatory conditions, including the autoimmune disorder rheumatoid arthritis, with anti-PSGL antibodies. Larsen teaches methods of treating a variety of conditions, including inflammatory disorders and autoimmune diseases with PSGL fusion proteins and anti-PSGL antibodies.

Snapp teaches that all T cells express high levels of PSGL-1, and that PSGL-1 is the principal ligand for P-selectin on T cells. Snapp *et al.*, p. 163. Diacovo teaches that PSGL is present on essentially all α/β T cells, although only about 54% of the α/β T cell population binds to P-selectin. Diacovo *et al.*, p. 1200. Diacovo does not teach whether the ability of approximately half the population of α/β T cells to bind P-selectin correlates with the expression of CD4 or CD8, or with the expression of any other antigen characteristic of a particular subset of α/β T cells. Finally, Diacovo also teaches that PSGL is present on about 74% of γ/δ T cells, and that about the same percentage (~80%) of the γ/δ T cell population binds to P-selectin. *Id.* Applicants note that γ/δ T cells do not express CD8, an antigen characteristic of cytotoxic T lymphocytes. The Examiner further cites both Raychaudhuri and Rooney for teaching a variety of well-known methods for determining CTL function, and alleges that Brenner provides both

further motivation to combine the cited references, and a reasonable expectation of success. 4/21/05 Office Action, p. 12.

Applicants respectfully submit that the combination of Snapp and Diacovo suggests only that PSGL-specific antibodies may be useful to inhibit P-selectin-mediated function of most or all T cells, whether α/β, γ/δ, CD4+, or CD8+. The combined references do not in any way suggest that PSGL-specific antibodies specifically target cytotoxic T lymphocytes (those expressing both the α/β form of the T cell receptor and the CD8 antigen). Neither the addition of Cummings and/or Larsen, nor of Raychaudhuri, Rooney, and Brenner to the combination remedies this deficiency. Therefore Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing remarks and amendments, Applicants respectfully request withdrawal of these rejections and timely allowance of the pending claims. Should the Examiner have remaining questions or concerns regarding this application, Applicants request that the Examiner contact the undersigned at 202-408-4086 to schedule an interview to discuss the application.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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